PAPER

Movement disorders in patients taking anticonvulsants

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J Neurol Neurosurg Psychiatry 2007;**78**:147–151. doi: 10.1136/jnnp.2006.100222

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Received 16 June 2006
Revised 7 September 2006
Accepted 9 September 2006
Published Online First 29 September 2006

Background: A wide variety of movement disorders may occur as a consequence of the administration of antiepileptic drugs (AEDs). Although it has been suggested that the risk of parkinsonism is 10-fold higher in those taking valproate as compared with other AEDs, there have been no large, systematic trials assessing this.
Aim: To establish more precisely the prevalence of and risk factors for developing parkinsonism associated with valproate use,and to assess the occurrence of movement disorders with the newer AEDs.
Methods: Patients with epilepsy were recruited from the Toronto Western Hospital Epilepsy Clinic (University of Toronto, Toronto, Ontario, Canada). Each patient was examined by a movement disorder specialist who was blinded to the treatment status of the patient.
Results: 201 patients were included. Postural tremor was the most common movement disorder (45%), followed by parkinsonism (4.5%). The odds of having parkinsonism were 5 times higher with valproate than with other AEDs. No single factor predicted the presence of parkinsonism; however, many (5/9) of the patients concurrently used other drugs or had comorbidities that could have caused or exacerbated parkinsonism. None of the newer AEDs were clearly associated with the presence of movement disorders; however, the numbers were too small to make a formal analysis.
Conclusion: Although the risk of parkinsonism with valproate is higher than with other AEDs, it is lower than originally reported. The cases available were not enough to accurately comment on the prevalence of movement disorders with the newer AEDs.

A wide variety of movement disorders may occur as a consequence of the administration of antiepileptic drugs (AEDs). Among the common movement disorders associated with AEDs, cerebellar ataxia is the most commonly reported, followed by asterixis and myoclonus, although a variety of others, including chorea, orofacial dyskinesias, tremor, tics and dystonia, can occur.[1–5] Most of the AEDs have been implicated at one time or another, with the most common offenders being phenytoin and carbamazepine, followed by valproate and phenobarbital.[6] Despite its utility, valproate commonly exerts side effects on the central nervous system (CNS). The most common is dose-related tremor, occurring in as many as one quarter of chronically treated patients.[7–11] Less often asterixis, chorea, sensorineural hearing loss and encephalopathy have been reported.[3 12 13] Although there have been case reports of parkinsonism induced by AEDs such as phenytoin[14 15] and carbazamepine,[16] the most common drug associated with parkinsonism by far is valproate.[6] Several case reports of valproate-induced parkinsonism, often accompanied by cognitive disturbances have been published.[11 17–21] A report of a multiple system atrophy-like syndrome is also available.[22] Both syndromes are said to resolve when the drug is withdrawn.[11 17 22] However, most studies have reported isolated cases and the few series looking at the prevalence of valproate-induced parkinsonism have been based on small sample sizes.[18 21] Moreover, there have been no recent systematic studies dealing with the prevalence of movement disorders related to new AEDs such as topiramate, vigabatrin, lamotrigine and gabapentin among others.

The primary purpose of this study was to establish more precisely the prevalence of and risk factors for developing valproate-induced parkinsonism. The secondary aim was to attempt to delineate the profile of new AEDs with regard to involuntary movement abnormalities. To avoid biases that may have influenced previous reports, we evaluated patients with epilepsy for the presence of movement disorders, blinded to the knowledge of which AEDs they were taking.

METHODS

A total of 205 consecutive patients were recruited from the Epilepsy Clinic at the Toronto Western Hospital (University of Toronto, Toronto, Ontario, Canada) during their routinely scheduled follow-up from March 2002 to February 2005. Patients were included if they were >18 years old, could provide informed consent, and were taking an AED for the treatment of epilepsy. Patients were excluded only if they were unable to give informed consent.

Each patient was examined by either CZ or RPM, who are fellows in movement disorders with at least 1 year of specialty training at the time of this study, who were blinded to the treatment status of the patient. All patients underwent a detailed neurological examination using a standardised protocol, which included a modified Unified Parkinson's Disease Rating Scale (UPDRS; all items of UPDRS III were assessed, but only the most involved hemibody (upper and lower limbs) was recorded for items 20, 21, 22, 23, 24, 25 and 26 for a total maximum score of 56), and a writing sample consisting of a standard sentence and tracing of the Archimedes spiral. Parkinsonism was defined as the presence of at least two of the following signs: rigidity, bradykinesia, postural instability and resting tremor with a UPDRS score of >10. A full history of drugs was taken for each patient independently of the movement disorders examination. The study was approved by the Toronto Western Hospital Research Ethics Board, and informed consent was obtained from all patients involved in the study.

Statistical analysis

The χ^2 test was used to test the significance of the presence of parkinsonism in those patients taking valproate versus those who were not. Parametric tests were used to assess the statistical significance of the difference in baseline

Abbreviations: AED, antiepileptic drug; CNS, central nervous system; UPDRS, Unified Parkinson's Disease Rating Scale

characteristics between these groups. The χ^2 and Fisher's exact test (if the values were <5) were used to test categorical variables, and t tests were used to compare continuous variables. For the multivariate analysis, logistic regression was then performed modelling the effects of age and duration of drug exposure to the development of parkinsonism. These same methods were then repeated to assess the development of other movement disorders.

RESULTS

In all, 205 patients were recruited. Four patients refused to participate, resulting in a total of 201 patients included in the study. Tables 1 and 2 outline the baseline characteristics and the frequency of AEDs used. In total, 42% of patients were taking a single drug, whereas 58% were on ⩾2 drugs. In the subgroup of patients taking valproate (59/201), 64.4% were taking ⩾2 drugs, whereas 35.6% were taking valproate alone.

By far the most common movement disorder seen was a postural/kinetic tremor (45%), followed by parkinsonism in 4.5% (n = 9) of the patients. We found four patients with dystonia, two with tics, one with akathisia and one with ataxia. No cases of myoclonus, asterixis or chorea were found. A total of eight patients were seen with a combination of movement disorders: tic and postural tremor (n = 2); parkinsonism and postural tremor (n = 5); parkinsonism and postural tremor with dystonia (n = 1). Avoiding double counts, the prevalence of movement disorders in this sample population was 48%, with tremor accounting for the largest proportion of patients.

Parkinsonism

Nine patients in the entire population had evidence of parkinsonism. No patient with a score of ⩽10 on the modified UPDRS had a score of >1 of 4 on any individual item, except possibly item number 21 (postural/action tremor of the hands). Six of the patients with parkinsonism were taking valproate, whereas the other three patients were taking various combinations of lamotrigine, vigabatrin, zonisamide and carbamazepine (table 3). Thus, in the entire sample, 10% of the patients taking valproate had features of parkinsonism compared with 2% of the patients taking other AEDs. The odds of having parkinsonism on taking valproate was 5.2 (95% confidence interval (CI) 1.26 to 21.733; p = 0.022). Symptoms were mild in all but one patient, who was the only patient having complaints related to parkinsonism and in whom the treating doctor had independently noted any parkinsonian signs. Only two of nine patients had a resting tremor; these patients also had postural/kinetic tremor, similar to the four of the remaining patients with parkinsonism. No significant difference was seen in the age of the patient, age at seizure diagnosis, polypharmacy, duration of valproate use, dose of valproate or sex among those who had parkinsonism while taking valproate versus those who did not (table 4). Even after adjusting for the age of the patient, there was no effect of duration of valproate use on the development of parkinsonism (p = 0.399).

Table 1 Baseline characteristics of sample population

Age (years)	40.55 (12.7; 19–78)
Age at diagnosis of epilepsy (years)	21.9 (15; birth–77)
Sex	
Male	92 (46)
Female	109 (54)
Polypharmacy, ⩾2 drugs	117 (58)
Seizure type	
Primary generalisation	41 (20.4)
Complex partial with/without secondary generalisation	134 (66.7)
Simple partial with/without secondary generalisation	24 (11.9)
Unclassified	2 (1)

Values are mean (SD; range) or n (%).

Table 2 Frequency of antiepileptic drugs used by the entire population (n = 201)

Drug	n (%)*
Valproate	59 (29.3)
Carbamazepine	79 (39.3)
Phenytoin	49 (24.4)
Topiramate	47 (23.4)
Clobazam	31 (15.4)
Lamotrigine	25 (12.4)
Phenobarbital	10 (5)
Gabapentin	9 (4.5)
Clonazepam	9 (4.5)
Vigabatrin	6 (3)
Levetiracetam	5 (2.5)
Primidone	5 (2.5)
Oxcarbazepine	3 (1.5)
Ethosuximide	3 (1.5)
Zonisamide	2 (1)
Acetazolamide	1 (0.5)
Lorazepam	1 (0.5)

*Percentages do not add up to 100 as 58% of patients were on multiple drugs.

Owing to the small number of outcomes, further predictors could not be analysed in the model. However, an extensive chart review of the patients with parkinsonism showed that, in >50% (5/9) of the patients, concurrent use of other drugs or medical conditions might have contributed to or caused the development of parkinsonism (table 3). For example, one patient was taking risperidone for at least 3 months before his assessment. A second patient had cerebral palsy due to a presumed perinatal injury with evidence of an old right-sided basal ganglia infarct. A third patient had neurofibromatosis with multiple lesions on brain magnetic resonance imaging. A fourth patient had a very atypical tremor with features suggestive of a psychogenic component (distractibility and variability of amplitude, frequency and direction). Finally, a fifth patient was diagnosed with coeliac disease 6 months before the onset of seizures, for which she was treated with valproate. Two years after starting valproate, in the setting of poor seizure control, she developed a ''sudden onset'' and slowly progressive cognitive decline characterised by a fronto-temporal pattern of dementia accompanied by stooped posture, bradykinesia and falls. Her seizure frequency eventually diminished; however, she remained moderately dependent in all her activities of daily living. Three years later, although still taking valproate, galantamine was started for dementia, and within a few months she was more alert and independent in her activities of daily living. Four years after the initial assessment for this study (1 year after starting galantamine), there was no longer any evidence of parkinsonism on neurological examination despite maintaining the original dosage of valproate. When these patients were excluded from the analysis, the odds of parkinsonism associated with valproate use diminished to 0.87 (95% CI 0.089 to 8.59).

Postural tremor

In all, 89 (45%) patients had a postural/action tremor. Of these, 70% were considered mild (having no interference with any activities), and 30% were considered moderate (having a mild interference with some activities) to severe (having interference with most activities). Valproate and carbamazepine were most commonly associated with tremor, followed by phenytoin. No

Table 3 Characteristics of patients with parkinsonism

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age (years)	55	49	42	43	44	61	39	29	51
Age at diagnosis of epilepsy (years)	46	27	7	27	Birth	53	5	23	Late teens
Sex	F	M	M	M	F	F	F	F	M
Anticonvulsant drugs at time of assessment	Carbamazepine, lamotrigine	Lamotrigine	Vigabatrin, zonisamide	Valproate, clobazam	Valproate	Valproate, gabapentin	Valproate	Valproate, carbamazepine	Valproate
UPDRS*	10.5	13	11	13	14	15	16	16.5	18
Duration on VPA (years)				2	7	4	2	13	16
Other movement disorders		Postural tremor			Postural tremor	Postural tremor	Postural tremor, dystonia	Postural tremor	Postural tremor
Other features of potential importance		Retinitis pigmentosa		Taking risperidone for 3 months at the time of assessment	Atypical tremor with variability and distractibility	Coeliac disease diagnosed 6 months before onset of seizures Acute onset, progressive cognitive decline 2 years after starting valproate	Cerebral palsy with mild left sided hemiparesis; left limbs smaller than right	Neurofibromatosis;	
Seizure type	Complex partial	Complex partial	Complex partial	Simple partial with secondary generalisation	Complex partial	Unclassified	Complex partial	Complex partial	Primary generalised

F, female; M, male; UPDRS, Unified Parkinson's Disease Rating Scale; VPA, valproate .
*Modified UPDRS III (all items of UPDRS III were assessed, but only the most involved hemibody (upper and lower limbs) was recorded for items 20, 21, 22, 23, 24, 25 and 26 for a total maximum score of 56).

relationship was found between the presence of postural tremor and the number of AEDs a patient was taking ($p = 0.94$). In all, six patients were found to have both a postural tremor and parkinsonism. Five of these patients were taking valproate (two in combination with another drug, gabapentin or carbamazepine) and one patient was taking lamotrigine.

Dystonia

On examination, four patients had evidence of dystonia. Two patients, a 28-year-old woman taking a combination of carbamazepine, clobazam and topiramate, and a 56-year-old man taking carbamazepine and valproate, had a focal, task-specific dystonia (writer's cramp). A 23-year-old woman taking topiramate had asymptomatic foot inversion, which became apparent with tasks of concentration/distraction. Finally, a 39-year-old woman receving valproate monotherapy had symptomatic left hemidystonia characterised by foot inversion and hand posturing. She also had signs of parkinsonism as well as a postural/action tremor that did not appear dystonic in nature. Her history was significant for cerebral palsy, and magnetic resonance imaging showed an old right-sided basal ganglia infarct, with bilateral caudate and putaminal atrophy. On questioning, only one patient in this group reported any difficulty in writing. This patient had generalised tonic–clonic seizures and multiple spells characterised by left-sided arm and leg posturing. At least some of these spells had been witnessed in the past, were distractible, and thus were considered partly non-organic.

Tics

Two patients had tics, both of whom manifested excessive eye blinking. The first patient was a 57-year-old man who was diagnosed with seizures at the age of 49 years and was taking a combination of phenytoin and clobazam. The second patient was a 47-year-old man who was diagnosed with epilepsy at the age of 12 years and was taking valproate. He also had a postural tremor. Neither of these patients nor their treating doctors were aware of the excessive blinking.

DISCUSSION

Valproate and parkinsonism

This is the first study to systematically examine patients taking a variety of AEDs in a blinded fashion to assess for the presence of movement disorders in this patient population. This is also the largest study to assess patients in this manner. The breakdown of seizure types is similar to that found in previous epidemiological studies,[23 24] and thus these patients are fairly representative of the general epilepsy population. In accordance with previous studies, valproate was the drug most commonly associated with a postural/action tremor,[7] followed by carbamazepine and phenytoin. The results of this study, like two previous studies, also suggest that the odds of having parkinsonism on taking valproate are higher than that on taking other AEDs. Although the mechanism of valproate-induced parkinsonism is not known, several biological theories have been proposed to explain this increased risk, including an effect on Complex I activity in the electron transport chain of mitochondria[18] and on GABAergic mechanisms in the basal ganglia.[26]

In the first clinical study, Armon *et al*[18] observed varying degrees of parkinsonism and cognitive impairment in 33 of 36 (92%) patients on valproate. In all, 27 of 36 (75%) patients had at least two of the cardinal features of parkinsonism. Valproate was discontinued in 32 of 33 affected patients and resulted in resolution of symptoms in all but one. In a second study, Easterford *et al*[21] examined 50 patients receiving valproate monotherapy for 1 year and compared them with 20 patients

Table 4 Parkinsonism in the valproate group (n = 59)

	UPDRS >10 (n = 6)*	UPDRS <10 (n = 53)*	p Value
Age at seizure diagnosis (years)	23.7 (19.4; 0–53)	19.1 (13.23; 29–67)	0.453
Duration on valproate (years)	7.8 (6.2; 2–17)	6.79 (5; 1–26)	0.639
Dose of valproate (mg)	1425 (354.6)	1209.9 (555.1)	0.359
UPDRS	15.5	1	<0.001
Age, years	43.5	37	0.195
Polypharmacy (⩾2 drugs)	50%	66.0%	0.406
Sex			0.671
Male	2	27	
Female	4	26	

Values are mean (SD; range), mean (SD) or median.
UPDRS, Unified Parkinson's Disease Rating Scale.
*UPDRS: modified UPDRS III (all items of UPDRS III were assessed, but only the most involved hemibody (upper and lower limbs) was recorded for items 20, 21, 22, 23, 24, 25 and 26 for a total maximum score of 56).

receiving carbamazepine monotherapy. Three patients in the valproate group (prevalence 6%) satisfied the criteria for parkinsonism. Although this was not significant, their results suggested a 10-fold increase in the incidence of parkinsonism in people taking valproate. Although all three studies highlight an increased risk of parkinsonism with valproate, our results suggest that the risk of parkinsonism associated with valproate use may not be as high as initially reported. Moreover, in most of the patients, another aetiology could be identified that may have either caused or exacerbated signs of parkinsonism. For example, one patient was taking risperidone, an atypical antipsychotic known to cause parkinsonism,[25] for at least 3 months before his assessment and a second patient had cerebral palsy due to a presumed perinatal injury, with evidence of an old right-sided basal ganglia infarct. It is well documented, that not only can the symptoms of cerebral palsy progress for many years after the initial insult, but also that anticonvulsant-induced movement disorders, including those induced by valproate, can occur in the setting of prior brain injury.[3] Finally, in the woman with coeliac disease and a frontotemporal pattern of dementia, parkinsonian symptoms resolved despite her continuing to take valproate, a course that has not, to date, been reported with valproate-induced parkinsonism. In fact, although no single factor seems to predict the development of parkinsonism while taking valproate, the odds of developing parkinsonism associated with valproate use drop dramatically when patients with possible alternatives (or contributing) aetiologies are excluded. Therefore, the presence of other comorbidites seems to play an important part. Finally, aside from the single patient in whom symptoms clearly began only after the initiation of valproate, parkinsonian symptoms had not been noted by the patients or their doctors, and therefore it is not known whether these are simply chance associations or whether a causal relationship does exist between valproate use and the presence of parkinsonism.

Other AEDs and movement disorders

Parkinsonism and dystonia were also seen in association with some of the newer drugs (eg, lamotrigine, zonisamide and vigabatrin). No previous reports on lamotrigine-induced parkinsonism exist in the literature. On the contrary, it was hoped that lamotrigine might exhibit antiparkinsonian effects through anti-glutamatergic activity. However, a double-blind placebo-controlled crossover trial failed to show antiparkinsonian effects in humans.[27] It has also been proposed that zonisamide might have antiparkinsonian effects, possibly due to the long-lasting activation of dopamine synthesis.[28]

Dystonia has been reported most commonly in patients taking carbamazepine and phenytoin.[29–31] Typically, this occurs in the setting of toxic drug levels or prior CNS injury,[30] and both focal (including writer's cramp)[32 33] and generalised dystonia[30] have been reported. In our series, two of the four patients with dystonia were taking carbamazepine, whereas one patient each was taking valproate and topiramate. Although dystonia has been described with valproate use in the past,[34] there are no reports of topiramate-induced dystonia, and in fact there is a single case report of a 46-year-old man with generalised dystonia, presumed to be due to a viral insult as a child, who responded to 200 mg/day topiramate.[35] Notably, only one of the four patients with dystonia was aware of any difficulties in writing and so it is impossible to deduce by history whether the dystonia was causally linked to these AEDs. In fact, this is unlikely in the patient with cerebral palsy. Therefore, no changes to the AED regimens were made on the basis of the examination findings. Moreover, there were so few events that conclusions about the risk of developing movement disorders while taking these newer AEDs cannot be drawn from this study.

Although the older literature highlighted ataxia and asterixis/myoclonus as the most common movement disorders caused by the AEDs,[6] there was only one patient with ataxia and no patients with asterixis/myoclonus in this series. These two movement disorders have been most commonly documented in the setting of intoxication with the offending drug.[36 37] The absence of such cases in this study may relate to closer monitoring and more cautious use of AEDs in recent years. Further, there is greater emphasis on rational polypharmacy, which may result in fewer instances of drug toxicity-induced adverse effects.

LIMITATIONS

This is the largest study to date to examine the occurrence of movement disorders in relation to AEDs, and unlike previous studies, the clinical evaluations were carried out by neurologists trained in movement disorders who were blinded to the drugs being taken by the patients. However, there are also limitations that must be mentioned. Given the small number of patients and the relative infrequency with which some of the AEDs were used, it is not possible to estimate the true prevalence of AED-associated movement disorders from this study. Moreover, patients were not examined before initiation of their AEDs, nor was valproate routinely withdrawn in those with signs of parkinsonism. This is because all patients, except for the one described above in whom a spontaneous remission of symptoms occurred, were asymptomatic and had adequate seizure control with their existing AED regimen. Therefore, it must be emphasised that it is impossible to determine whether the observed associations are causal or simply coincidental.

CONCLUSION

Although the risk of parkinsonism associated with valproate use is higher than that with other AEDs, it is probably lower than previously reported and other factors probably play an important role. The number of cases available was not sufficient to accurately comment on the prevalence of movement disorders with the newer AEDs. Further prospective studies will need to be undertaken to define better the role of the various AEDs in the development of movement disorders.

ACKNOWLEDGEMENTS

Dr Zadikoff is an American Academy of Neurology Foundation Clinical Research Fellow.

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Competing interests: None.

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